REMARKS

Claims 1-38 are currently pending in this application. Claims 1-9 were cancelled by the Response to Restriction Requirement filed May 9, 2002, and Claims 31-38 were cancelled by the Amendment filed September 25, 2002. Therefore, Claims 10-30 are presently under examination and stand rejected.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 10-30 were all rejected in the December 2, 2002, Office Action under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such as way as to enable one skilled in the art to make and use the invention. It is the Examiner's position that Claims 10-30 fail to meet the standards for enablement as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The Examiner specifically points to six of the eight factors of *In re Wands*, and asserts that when they are weighed, one skilled in the art would be unable to practice this invention without undue experimentation. Applicants respectfully traverse this rejection for the reasons provided herein.

1. The Nature of the Invention. The Examiner states in the December 2, 2002, Office Action that the claimed invention is drawn to a method of treating angiogenesis by 2-substituted estradiol derivatives of the formula in Claims 10 and 19.

Applicants respectfully maintain that Examiner's statement is incomplete. The claimed invention is drawn to a method of treating angiogenesis comprising administering to an endothelial cell an angiogenesis inhibiting amount of an analog or derivative of estradiol that is modified at the 2-carbon *and* the 16-carbon. In particular, every claim of the present invention

comprises a 2- *and* 16-substituted compound, wherein the 17-carbon (>C-R_g) is always >C(H)-OH. In Claim 10, the steroid compound may be *optionally* substituted at the 1-, 3-, 4-, and 6-carbons.

Claim 11 is drawn to a series of 16-substituted *2-methoxyestradiol* compounds. Claims 12-18, which depend from Claim 11, define specific R_{h1} and R_{h2} substituents, therefore Claims 12-18 are each drawn to a single compound.

Similarly, Claim 19 is drawn to a series of 2- *and* 16-substituted *estradiol* compounds. Claims 20-30, which depend from Claim 19, are also drawn to a series of 2- and 16-substituted estradiol compounds in which the 2-substituent (R_a) is specified, and the substituents R_{h1} and R_{h2} are defined as in Claim 19.

Applicants respectfully maintain that the Examiner's statement regarding the nature of the invention is incomplete and provides no basis for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled.

2. The State of the Prior Art. According to the December 2, 2002, Office Action, it is the Examiner's position that the prior art of record teaches a method of treatment of angiogenesis using, for example, 2-methoxy estradiol, 2-ethoxy estradiol, 2-alkoxyestradiol derivatives, and estrone, 2-hydroxyalkylestradiols, 2-methoxyoestrone-3-*O*-sulfamate. The Examiner states that all the compounds are estradiol or estrone derivatives known to treat angiogenesis or cancer.

Applicants respectfully maintain that the Examiner's statement provides no basis for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled. Rather, Applicants note that if, as the Examiner states, estradiol or estrone derivatives are known to treat

angiogenesis or cancer, any pharmaceutical formulations, any dosing schedules, or any other relevant information known regarding these derivatives would provide support for Claims 10-30 of the present invention being fully enabled, because such information would be available to one of ordinary skill at the time the invention was made.

Therefore, Applicants respectfully maintain that the Examiner's statement regarding derivatives known to treat angiogenesis or cancer provides no basis for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled, but rather supports their enablement.

3. The Predictability in the Art. As stated in the December 2, 2002, Office Action, it is the Examiner's position that there is a general lack of predictability in the pharmaceutical art, and the unpredictability of the steroid art is very high. The Examiner points to the following evidence.

a. *Applicants' Specification, page 20, lines 20-25 (Table 1).* It is the Examiner's position that the relative antiproliferative activities of 2-methylhydroxy estradiol, 2-formyl estradiol, and 2-acetyl estradiol presented in Table 1 (*see* specification, page 20) are indicative of the high unpredictability of the steroid art. The Examiner uses this antiproliferative data as support that method of Claims 10-30 fails to meet the standards for enablement as set forth in *In re Wands*. The Applicants respectfully traverse the Examiner's conclusion for the following reasons.

Table 1 (specification, page 20, lines 20-25) summarizes the results of three (3) different assays that are useful in determining and predicting the antiproliferative and antitumor

activity of the compounds, namely the IC_{50} values in HUVEC cells, the IC_{50} values in MDA-MB-231 cells, and the Proliferation Index in estrogen dependant MCF-7 cells. As seen from these data, all of the 2-modified analogs presented in Table 1 have significantly lower estrogenic activity than estradiol, as indicated by the MCF-7 cell Proliferation Index. Further, all of these compounds exhibited antiproliferative or antitumor activity in at least one assay. Both the 2-methylhydroxy and 2-formyl derivatives had good antiproliferative activity in HUVEC cells, while the 2-acetyl E2 had good activity in breast tumor MDA-MB-231 cells. Therefore, Applicants respectfully assert that Table 1 *supports* the enablement of Claims 10-30 by indicating what type of antiproliferative or antitumor activity to look for in screening the claimed compounds.

Accordingly, Applicants respectfully assert that the specification clearly and concisely indicates standard tests that allow rapid screening and identification of the claimed compounds that exhibit angiogenesis inhibiting activity. Therefore, Applicants respectfully maintain that Table 1 provides no basis or support for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled, but rather *supports* the enablement of Claims 10-30 by indicating what to look for.

b. *The Predictable Activity of the Compounds of Claims 10 and 19.* It is the Examiner's position that it is not obvious from the disclosure of one species what other species will work. In support of this position, the Examiner cites *In re Dreschfield* 110 F.2d 235, 45 USPQ 36 (CCPA 1940) for the general rule, "...in cases involving chemicals and chemical compounds, which differ radically in their properties, it must appear in an applicant's specification either by enumeration of a sufficient number of the members of a group or by other

appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."

Applicants respectfully maintain that the *In re Dreschfield* rule is not applicable to Applicants' Claims 10 and 19, and therefore cannot constitute a basis for an non-enablement rejection, for the following reasons. Applicants respectfully assert that the genera provided in Claims 10 and 19 do not encompass chemical compounds "which differ radically in their properties" according to *In re Dreschfield.* The claimed invention is drawn to a method of treating angiogenesis comprising administering an angiogenesis inhibiting amount of an analog or derivative of estradiol that is modified at the 2-carbon *and* the 16-carbon. In particular, every claim of the present invention comprises a 2- *and* 16-substituted compound, wherein the 17-carbon (>C-R_g) is always >C(H)-OH. Applicants assert that these compounds do not constitute unrelated members of a Markush group, but rather are structurally and chemically related.

Further, even if the *In re Dreschfield* rule were applicable to Applicants' Claims 10 and 19, Applicants respectfully assert that Applicants' specification provides both: 1) enumeration of a sufficient number of the members of a group; and 2) other appropriate language indicating that the compounds included in the claims are capable of accomplishing the desired result. First, Claims 12-18 are each drawn to a single 16-substituted 2-methoxyestradiol compound, and Table 2 (Example 24, page 33) discloses the antiangiogenic and antitumor activity of each compound. Claim 19 is drawn to a series of 2- and 16-substituted estradiol compounds in which *only* the 2- and 16-substituents vary. Claims 20-30, which depend from Claim 19, are drawn to a series of 2- and 16-substituted estradiol compounds, which utilize the *same* 16-substituents as in Claims 10 and 11 and Table 2, in which each of Claim 20 to 30 is drawn to a group of compounds with a *single* 2-substituent. Therefore, Applicants respectfully

assert that by numerous examples *and* by appropriate language, the compounds encompassed by this invention capable of accomplishing the desired inhibition of angiogenesis are clearly enumerated.

Moreover, the specification suggests one reason, among others, why the compounds disclosed therein were selected for testing. Since 2-methoxyestradiol is metabolized to a much less active metabolite, the present invention adds steric bulk and/or modification of electrostatic characteristics at the 16-carbon of 2-methoxyestradiol for retarding or preventing interaction of 17β-hydroxysteroid dehydrogenases and co-factor $NADP^+$ on this substrate. Addition of steric bulk and/or modification of electrostatic characteristics at the 16-carbon of 2-methoxyestradiol may retard or prevent glucuronidation. It is believed that retardation or prevention of these two metabolic deactivation pathways prolongs the serum lifetime of 2-methoxyestradiol and other estrogenic compounds while retaining the desired anti-angiogenic and anti-tumor activity. *See* specification, page 11, lines 16-27. Indeed, initial screening of epimeric 16-ethyl-2-methoxyestradiol and related analogues showed that it is about equipotent to 2-methoxyestradiol in inhibition of HUVEC cell proliferation *in vitro*. *See* specification, page 17, lines 2-6.

Further, Applicants respectfully maintain that the specification (page 20, lines 20-25; Examples 23 and 24, pages 31-34) provides at least three (3) different assays that are useful in determining and predicting the antiproliferative and antitumor activity of the compounds, namely the IC_{50} values in HUVEC cells, the IC_{50} values in MDA-MB-231 cells, and the Proliferation Index in estrogen dependant MCF-7 cells. The specification further indicates that all of these compounds exhibited antiproliferative or antiangiogenic activity in at least one of the assays.

Applicants further assert that *additional* assays are disclosed in the specification that are useful in determining and predicting the antiangiogenic activity of the compounds. For example, the specification discloses the chick embryo chorioallantoic membrane (CAM) assay as a suitable assay for angiogenesis inhibiting activity for compounds of the present invention. *See* specification, page 12, lines 1-17. Pharmaceutical formulations and dosages of the compounds are also disclosed. *See* for example, specification page 17, line 8-page 19, line 20.

Accordingly, Applicants respectfully maintain that the specification has clearly delineated a basis for selecting species that exhibit and are expected to inhibit angiogenesis. Accordingly, Applicants respectfully maintain that *In re Dreschfield* provides no basis for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled.

c. *Sufficient Number of Representative Examples.* The Examiner states that the disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds within the scope of a claim will possess the alleged activity. The Examiner further states that, "predicting the activity of all the estradiol derivatives as in Claims 10 and 19 is impossible."

Applicants respectfully submit that numerous representative examples have been provided in Examples 1-24, including Table 2, which provide reasonable assurance that the compounds of the present invention will possess the desired activity. Table 2 of the specification discloses numerous 16-substituted 2-methoxyestradiol compounds of the present invention, along with data regarding their antiproliferative, antiangiogenic, and antitumor activity. *See* Example 24, page 33; Claims 11-18. Both HUVAC (Example 24) and MDA-MB-231 (Example 23) *in vitro* cellular proliferation inhibition assays are disclosed in the specification as means to test the

compounds according to the present invention. *See* specification, pages 31-34. The specification further discloses the chick embryo chorioallantoic membrane (CAM) assay as a suitable assay for angiogenesis inhibiting activity for compounds of the present invention. *See* specification, page 12, lines 1-17. Pharmaceutical formulations and dosages of the compounds are also disclosed. *See* for example, specification page 17, line 8-page 19, line 20.

Applicants are not aware of any provision in the MPEP requiring Applicants to predict the activity of all the estradiol derivatives of Claims 10 and 19. Respectfully, Applicants submit that the inability to make such predictions does not constitute a proper ground for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph. *See* MPEP § 2164.01 *et seq.* Regarding this issue, MPEP 2164.01(b) provides that, "...it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph."

Applicants maintain that the specification discloses numerous representative examples which provide more than reasonable assurance to one skilled in the art that the compounds within the scope of a claim possess the desired activity. The specification also provides standard tests for screening and identification of the claimed compounds that exhibit angiogenesis inhibiting activity, along with pharmaceutical formulations and dosages of the compounds. Screening of compounds using the tests disclosed in the present application does not constitute undue experimentation. Therefore, Applicants respectfully submit that the

Examiner's assertion is incorrect and provides no ground for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled.

4. The Presence or Absence of Working Examples. The Examiner states, as set forth in the December 2, 2002 Office Action, that there is no data for compounds having a variety of substituents at the 1-, 2-, 3-, 4-, 6-, 16-, or 17-carbons that would assist the skilled artisan in practicing the claimed invention. The Examiner states that the skilled artisan would be at a loss as to where to begin such discovery in the absence of such data.

Applicants respectfully maintain that the Examiner's assertion is not correct because numerous working examples and considerable activity data for many 2-, 16-, and 17-substituted compounds are disclosed, that would enable the skilled artisan to practice the claimed invention. For example, Table 2 of the specification discloses several 16-substituted 2-methoxyestradiol compounds of the present invention, along with data regarding their antiproliferative and antiangiogenic activity. *See* Example 24, page 33; Claims 11-18. Applicants also note that both MDA-MB-231 (Example 23) and HUVAC (Example 24) *in vitro* cellular proliferation inhibition assays are disclosed in the specification as means to test the compounds according to the present invention for their antiangiogenic activity. *See* specification, pages 31-34. The specification further discloses the chick embryo chorioallantoic membrane (CAM) assay as a suitable assay for angiogenesis inhibiting activity for compounds of the present invention.. *See* specification, page 12, lines 1-17. Pharmaceutical formulations and dosages of the compounds are also disclosed in the specification. *See* for example, specification page 17, line 8-page 19, line 20.

Respectfully, Applicants further submit that the presence of working examples is in fact not required. Applicants submit that the specification contains examples illustrating the relative antiangiogenic and antiproliferative activities of 2-methylhydroxy estradiol, 2-formyl estradiol, and 2-acetyl estradiol (*see* Table 1, page 20), as well as antiangiogenic and antiproliferative data for several 16-substituted 2-methoxyestradiol compounds. Therefore one skilled in the art would predict following those examples that other claimed 2- and 16-substituted analogs of 2-methoxyestradiol would inhibit angiogenesis. "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." MPEP 2164.02; *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed Cir. 2987) (quoting *In re Chilowsky*, 229 F.2d 457, 461 (CCPA 1956).

Therefore, Applicants respectfully maintain that the Examiner's assertion of lack of data is incorrect, and does not constitute a ground for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph.

5. The Breadth of the Claims. It is the Examiner's position, as set forth in the December 2, 2002, Office Action, that the claims of the present invention are drawn to a method of treating angiogenesis using hundreds of compounds as provided in Claims 10 and 19, therefore these claims are considered broad.

The Applicants respectfully assert that the scope of the *enablement* provided by the disclosure is *commensurate with the scope of the protection sought* by the claims. *See* MPEP § 2164.08; *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). Accordingly, claim breadth is itself an insufficient ground for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled. *See* MPEP § 2164.08.

The claimed invention is drawn to a method of treating angiogenesis comprising administering to an endothelial cell an angiogenesis inhibiting amount of an analog or derivative of 2-methoxyestradiol that is modified at the 2-carbon *and* the 16-carbon. In particular, every claim of the present invention comprises a 2- *and* 16-substituted compound, wherein the 17-carbon (>C-R_g) is always >C(H)-OH. In Claim 10, the steroid compound may *optionally* be substituted at the 1, 3, 4, and 6-positions.

Synthetic approaches to all possible substituted compounds are presented in the specification. *See* page 15, line 30-page 17, line 6. MDA-MB-231 (Example 23) and HUVAC (Example 24) *in vitro* cellular proliferation inhibition assays are disclosed to test the compounds according to the present invention for their antiangiogenic activity. *See* specification, pages 31-34. The chick embryo chorioallantoic membrane (CAM) assay is also disclosed as a suitable assay for angiogenesis inhibiting activity for compounds of the present invention. *See* specification, page 12, lines 1-17. Further, pharmaceutical formulations and dosages of the compounds are disclosed. *See* for example, specification page 17, line 8-page 19, line 20.

Accordingly, Applicants maintain that the scope of the enablement in the disclosure is *fully commensurate* with the scope of the protection sought by the claims, and respectfully assert that the Examiner's assertion of claim breadth does not provide a proper basis for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled.

6. The Quantity of Experimentation Needed. It is the Examiner's position that: *i)* the nature of the method claimed is so unpredictable; *ii)* the claims are drawn to a broad range of pharmaceuticals for treating angiogenesis; and *iii)* there is a general lack of guidance present in the specification, that the skilled artisan would require undue experimentation to practice the

claimed invention. In particular, the Examiner states that the biological activity of an estradiol derivative cannot be predicted *a priori*, but must be determined case-by-case by resorting to an undue, "painstaking experimental study", to determine if the estradiol derivative shows angiogenesis activity. Respectfully, Applicants traverse this statement for the following reasons.

Applicants respectfully submit that at the time of their invention, one of ordinary skill in the art could readily practice Applicants' invention without undue experimentation. Applicants submit that enablement is not precluded by the necessity for some experimentation, such as routine screening. *John Hopkins Unvi. v. CellPro, Inc.*, 152 F.3d. 1342 (Fed. Cir. 1998). "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." *Id.* at 1360. Thus, the fact that some experimentation is necessary is permissible.

Applicants invention is directed towards the treatment of angiogenesis and angiogenesis-dependent disorders, thus it was necessary to determine if a compound of Applicants' invention inhibits angiogenesis. Applicants submit that once the anti-angiogenic activity of a compound is determined, it is merely routine testing, for one of ordinary skill in the art, to examine the angiogenic inhibition for a particular disease in a suitable test model, using histological techniques. For example, it was known that proliferative retinopathy, which mimics the neovascular component of acute retinopathy of prematurity, could be developed in new born mice exposed to high (> 98%) ambient oxygen during the new born period. *See Gole et al., "The Mouse Model of Oxygen-Induced Retinopathy: A Suitable Model for Angiogenesis Research,"*

Doc. Ophthalmol. (1990) 74(3): 163-169. Stimulation of wound healing could be studied in rats by repeated localized administration of brain extract from cattle containing fibroblast growth factor activity. *See Buntrock et al., "Stimulation of Wound Healing Using Brain Extact with Fibroblast Growth Factor (FGF) Activity. II. Histological and Morphometric Examination of Cells and Capillaries," Exp. Pathol.* (1982) 21(1):62-67. An experimental model was also developed to study macular degeneration. *See Ryan, S.J., "The Development of an Experimental Model of Subretinal Neovascularization in Disciform Macular Degeneration," Trans. Am. Opthalmol. Soc.* (1979) 77:707-745. Applicants incorporated by reference U.S. Patent No. 5,001,116 (see page 5, line 28) which discloses that inflammatory angiogenesis can be induced by the implantation of silica particles into a rabbit cornea, and that immune angiogenesis can be induced by the implantation of the lymph node of a different rabbit (see column 12, lines 6-9 of 5,001,116). This patent also discloses an animal model for the study of angiogenesis in tumor vessels. Moreover, since human subjects cannot be treated with new experimental drugs, the new drug must be tested on animal or *in vitro* models.

The specification also discloses the use of the chick embryo choriollantoic membrane (CAM) assay to test the compounds of Applicants' invention. *See* specification, page 12, lines 1-17. This assay, a standard screening test to determine anti-angiogenic activity, was known in the art at the time of Applicants' invention. *See Folkman, J. et al.,* Angiogenesis," *J. Biol. Chem.* (1992) 276(16), page 10932. Although the assay was implemented with only one representative compound, 2-methoxyestradiol, the assay serves as the test for all of the compounds of Applicants' invention, including the 16-substituted 2-methoxyestradiol compounds.

The extensive experimental data showing the anti-angiogenic activity of compounds disclosed in this invention, using HUVEC cells (*See* Example 24) and MDA-MB-231 cells (*See* Example 23) and proliferation index in estrogen dependant MCF-7 cells, supports the use of 2- and 16-substituted estradiol derivatives as an anti-angiogenic agents, in accordance with the disclosure in the specification. Moreover, the similarity among the estradiol derivatives claimed *and* tested and those claimed for which no test data are available, would lead one skilled in the art to expect all the claimed compounds would, like 2-methoxyestradiol, inhibit the formation of new blood vessels. Additionally, the specification discloses formulations and routes of administration for compositions based on 2-methoxyestradiol, and the other compounds disclosed in the specification. *See* specification page 17, line 8-page 19, line 20. Variations of such parameters are well within the skill of the ordinary artisan, as is the choice of a suitable test model for a particular disease.

Thus, Applicants respectfully submit that the specification is fully enabled. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusion

Applicants respectfully maintain that it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above *In re Wands* factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. MPEP 2164.01(a); *In re Wands* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. Applicants respectfully assert, on the basis of the arguments presented herein, that none of the *In re Wands* factors presented by the Examiner, whether considered individually or collectively, provides a ground for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled.

In view of the above remarks, Applicants respectfully maintain that Claims 10-30 are fully enabled and hence are in condition for allowance. Such action is respectfully requested. If there are informalities remaining in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at 404.745.2420 is respectfully solicited.

Respectfully submitted,

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